OCT 8 1999

NDA 18-972/S-019
S-020

Wyeth Laboratories
Attention: Ms. Roberta R. Acchione
170 North Radnor-Chester Road
St. David's, PA 19087-5221

Dear Ms. Acchione:

Please refer to your supplemental new drug applications dated August 27, 1998 (S-019) and December 23, 1998 (S-020), received August 28, 1998 and December 28, 1998, respectively, submitted under section 505(b)
of the Federal Food, Drug, and Cosmetic Act for Cordarone (amiodarone HCl) Tablets, 200 mg.

We acknowledge receipt of your submissions dated March 9 (S-020), May 3, July 14, and August 31, 1999 (S-019 and S-020).

Supplemental application 019 provides for final printed labeling revised to add a **Geriatric Use** subsection under **PRECAUTIONS** section of the labeling. In addition, revisions have been made in the **CLINICAL PHARMACOLOGY/Pharmacokinetics** subsection to bring Cordarone Tablet labeling into accord with the Cordarone I.V. labeling.

The changes in supplemental application 020 are contained in the same final printed labeling as 019 and provides for revised text under the **CLINICAL PHARMACOLOGY/ Pharmacokinetics** subsection and the **DOSAGE AND ADMINISTRATION** section to incorporate results of the effect of food on the oral administration of aniiodarone.

The following changes in the labeling have been made:

1. Under **CLINICAL PHARMACOLOGY/Pharmacokinetics,**

   a. The following has been added at the end of the first paragraph:

      Food increases the rate and extent of absorption of Cordarone. The effects of food upon the bioavailability of Cordarone have been studied in 30 healthy subjects who received a single 600-mg dose immediately after consuming a high fat meal and following an overnight fast. The area under the plasma concentration-time curve (AUC) and the peak plasma concentration (C_{max}) of amiodarone increased by 2.3 (range 1.7 to 3.6) and 3.8 (range 2.7 to 4.4) times, respectively, in the presence of food. Food also increased the rate of absorption of amiodarone, decreasing the time to peak plasma concentration (T_{max}) by 37%. The mean AUC and mean Cmax of desethylamiodarone increased by 55% (range 58 to 10 1%) and 32% (range 4 to 84%), respectively, but there was no change in the T_{max} in the presence of food.

b. The third and fourth sentences of the second paragraph in the **Pharmacokinetics** subsection have been deleted and replaced with three other sentences. This paragraph has been changed from:

Cordarone has a very large but variable volume of distribution, averaging about 60 L/kg, because of extensive accumulation in various sites, especially adipose tissue and highly perfused organs, such as the liver, lung, and spleen. One major metabolite of Cordarone, desethylamiodarone, has been identified in man; it accumulates to an even greater extent in almost all tissues. The pharmacological activity of this metabolite, however, is not known. During chronic treatment, the plasma ratio of metabolite to parent compound is approximately one.

to:

Cordarone has a very large but variable volume of distribution, averaging about 60 L/kg, because of extensive accumulation in various sites, especially adipose tissue and highly perfused organs, such as the liver, lung, and spleen. One major metabolite of Cordarone, desethylamiodarone (DEA), has been identified in man; it accumulates to an even greater extent in almost all tissues. No data are available on the activity of DEA in humans, but in animals, it has significant electrophysiologic and antiarrhythmic effects generally similar to amiodarone itself. DEA's precise role and contribution to the antiarrhythmic activity of oral amiodarone are not certain. The development of maximal ventricular class III effects after oral Cordarone administration in humans correlates more closely with DEA accumulation over time than with amiodarone accumulation.

c. The third paragraph of the **Pharmacokinetics** subsection has been changed from:

The main route of elimination is via hepatic excretion into bile, and some enterohepatic recirculation may occur. However, its kinetics in patients with hepatic insufficiency have not been elucidated. Cordarone has a very, low plasma clearance with negligible renal excretion, so that it does not appear necessary to modify the dose in patients with renal failure. In patients with renal impairment, the plasma concentration of Cordarone is not elevated. Neither Cordarone nor its metabolite is dialyzable.

to:

Amiodarone is eliminated primarily by hepatic metabolism and biliary excretion and there is negligible excretion of amiodarone or DEA in urine. Neither amiodarone nor DEA is dialyzable.

In clinical studies of 2 to 7 days, clearance of amiodarone after intravenous administration in patients with VT and VP ranged between 220 and 440 mL/hr/kg. Age, sex, renal disease, and hepatic disease (cirrhosis) do not have marked effects on the disposition of amiodarone or DEA. Renal impainnent does not influence the pharmacokinetics of amiodarone. After a single dose of intravenous amiodarone in cirrhotic patients, significantly lower Cmax and average concentration values are seen for DEA, but mean amiodarone levels are unchanged. Normal subjects over 65 years of age show lower concentrations (about 100 ml/hr/kg) than younger subjects (about 150 ml/hr/kg) and an increase in **t1/2** from about 20 to 47 days.

In patients with severe left ventricular disposition the pharmacokinetics of amiodarone are not significantly altered but the terminal disposition $\mathbf{t_{1/2}}$ of DEA is prolonged. Although no dosage adjustment for patients with renal, hepatic, or cardiac abnormalities has been defined during chronic treatment with Cordarone, close clinical monitoring is prudent for elderly patients and those with severe left ventricular dysfunction.

d. The following has been added at the beginning of the fifth paragraph:

Following single dose administration in 12 healthy subjects, Cordarone exhibited multi-compartmental pharmacokinetics with a mean apparent plasma terminal elimination half-life of 58 days (range 15 to 142 days) for amiodarone and 36 days (range 14 to 75 days) for the active metabolite (DEA).

2. Under **PRECAUTIONS**, a new Geriatric Use subsection has been added that states:

Geriatric Use
Clinical studies of Cordarone Tablets did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

3. Following the second sentence of the second paragraph under **DOSAGE AND ADMINISTRATION,** the statement that "Because of the food effect on absorption, Cordarone should be administered consistently with regard to meals (see '**Clinical Pharmacology'**)" has been added. The second paragraph now states:

In order to insure that an antiarrhythmic effect will be observed without waiting several months, loading doses are required. A uniform, optimal dosage schedule for administration of Cordarone has not been determined. Because of the food effect on absorption, Cordarone should be administered consistently with regard to meals (see **"Clinical Pharmacology")** Individual patient titration is suggested according to the following guidelines.

We have completed the review of these supplemental applications, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the submitted final printed labeling (package insert included in your August 31, 1999 submission). Accordingly, these supplemental applications are approved effective on the date of this letter.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

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If you have any questions, please contact:

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Sincerely yours,

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